

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-567

CORRESPONDENCE

Food and Drug Administration
Rockville, MD 20857

IND

Bristol-Meyers Squibb Company
Attention: Cynthia F. Piccirillo
Associate Director, Regulatory Science
5 Research Parkway
Wallingford, CT 06492


Dear Ms. Piccirillo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-232632. As a follow-up to our teleconference regarding the generic name, atazanavir, for BMS-232632, we would like to restate our position. As previously communicated to you during our September 17, 2001 teleconference, we have concerns regarding the use of the generic name, atazanavir and potential drug errors that may arise due to its similarity with the generic name, zanamavir (Relenza®), an antiviral drug indicated for the treatment of influenza. At that time, we did not require that Bristol-Myers Squibb (BMS) take any action and left the decision to request a new generic name to the Sponsor. Our position has not changed and we continue to have concerns regarding the name, atazanavir. However, the Division's concerns do not reach the level where we would take regulatory action against an application submitted with atazanavir as the United States Adopted Name (USAN). We leave the decision to negotiate with the International Nonproprietary Names (INN) to you, emphasizing that this does not imply support of the name atazanavir.

Although we acknowledge the use of the generic name, atazanavir, in the medical literature and community, we wish to remind you of 21 CFR 299.4 (d). The last sentence of this regulation states, "Prior use of a name in the medical literature or otherwise will not commit the Food and Drug Administration to adopting such terminology as official." Should you decide to change the generic name, we understand that it may take some time and would not expect you to change any documents already drafted.

If you have any questions, call Karen Young, Regulatory Project Manager, at 301-827-2335.

Sincerely yours,


{See appended electronic signature page}

Debra B. Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research



Food and Drug Administration
Rockville MD 20857

IND _____

Bristol-Myers Squibb Company
Attention: Louis Ferrara
Director Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Mr. Ferrara:

Please refer to your Investigational New Drug Application (IND) _____ submitted under 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-232632 for the treatment of HIV infection, and to BMS Study AI 424-008, a study of your experimental protease inhibitor BMS-232632.

The purpose of this letter is to address your non-compliance with the requirements for reporting of Serious Adverse Events (SAE's) and deaths as outlined in 21 CFR 312.32.

We have recently become aware that patient 40-154 enrolled in Study AI424-008 experienced a series of SAE's culminating in death. These SAE's included peripheral neuropathy, progressive weakness, dysphagia, dilated cardiomyopathy, hepatic steatosis, lactic acidosis, and death. Although the events immediately preceding this patient's death (hepatic steatosis and lactic acidosis) can be attributed to nucleoside analogue therapy, our interpretation of these events is that they were unexpected and could have been possibly associated with BMS-232632.

This patient death was reported via MedWatch (Report # 3726418) to NDA 20-412, four months after the death occurred. Records indicate that you failed to notify the Agency via telephone or facsimile transmission and failed to submit any written reports outlining these events and death to IND _____

We would like to remind you of your responsibilities under the Code of Federal Regulations (21 CFR.312.32)(c)(2) which state, "*Telephone and facsimile transmission safety reports*. The sponsor shall also notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information."

Additionally, we would like to bring to your attention to 21 CFR regulation 312.32(c)(1)(i), which state, "*IND safety reports. Written reports*. The Sponsor shall notify FDA and all participating investigators in a written IND safety report of: (A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or (B) Any finding from tests in laboratory animals that suggests a

significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information."

We would like to bring your attention to 21 CFR regulation 312.32(a) which defines a *Serious adverse experience* as: "Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition." Even though nucleoside analogues have been associated with lactic acidosis, BMS-232632 is an investigational drug and its safety profile is as yet unknown. Therefore, a conservative interpretation of these events would be prudent.

Please review all active studies of BMS-232632 and provide line reports of any SAE's not previously submitted to the Division of Antiviral Drug Products. In addition, please provide a summary and detailed analysis of all SAE's and deaths that have occurred in studies of BMS-232632. We expect you to submit your response regarding this serious lapse in reporting within four weeks of your receipt of this letter.

In the past, when the Division has had concerns regarding attribution of causality of serious adverse events, we have requested all SAE's quarterly. At this time, we would like to request that you provide us with a quarterly report of all SAE's.

If you have any questions, please contact Karen Young, Regulatory Project Manager, at 301-827-2335.

Sincerely yours,



Debra B. Birnkrant
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

IND

Bristol-Myers Squibb Company
Attention: Sherry Konrad
Senior Regulatory Affairs Associate
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Konrad:

Please refer to your investigational new drug (IND), submitted under 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-232632 for the treatment of HIV-1 infection.

The purpose of this correspondence is to encourage all sponsors with antiretroviral drugs in development to conduct studies in treatment-experienced HIV-infected individuals and to promote pharmaceutical collaboration to meet this objective. As you are aware, accelerated approval regulations (21 CFR 314.500) provide an approval mechanism for products used to treat serious and life-threatening illnesses that represent improvements over available therapy, or treatments for individuals who have exhausted existing options. Thus, it is expected that most new drug applications for antiretrovirals submitted under the accelerated approval mechanism will include some clinical data in patients with limited treatment options.

Scientific data clearly support the principle that HIV should be treated with combination therapy to maintain durable virologic suppression. Whenever possible, all trial participants should have the opportunity to receive combination therapy with several potentially active drugs. Therefore, in studies involving patients with limited approved treatment options, combining multiple investigational agents may be necessary. We would like to clarify that neither the Division of Antiviral Drug Products (DAVDP) nor the regulations prohibit the use of more than one investigational agent in a clinical trial or expanded access program. In fact, DAVDP encourages the study and/or treatment use of multiple investigational agents as appropriate for patients with limited treatment options.

However, when including multiple investigational drugs in phase 3 pivotal trials, the division recommends that the study design be such that the contribution of the investigational agent(s) of interest can be distinguished. We feel that this can be reasonably accomplished through "factorial" comparisons. The division will also accept other design proposals in which investigational drug activity and safety can be isolated. Study design and statistical methods for analyzing such studies should be discussed with the division in advance. In addition, potential drug-drug interactions among investigational agents should be sufficiently understood prior to initiation of a large study to avoid inappropriate dosing or safety risks due to overlapping toxicities.

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We will be happy to discuss any new protocol proposals for the study of heavily pre-treated patients with BMS-232632 in combination with approved or other investigational drugs and will be appreciative of pharmaceutical collaboration in the development of innovative trial designs in the study of this patient population.

If you have any questions, please contact Ms. Melissa M. Truffa, R.Ph., Regulatory Project Manager at 301-827-2335.

Sincerely yours,

A stylized handwritten signature, likely of Heidi Jolson, consisting of a vertical line followed by a large, bold 'S' and a final vertical stroke.

Heidi Jolson, M.D., M.P.H.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

INC _____
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Concurrence:

HFD-530/DepDir/Birnkrant

HFD-530/MTL/Cvetkovich

HFD-530/MO/Toerner

HFD-530/CPMS/DeCicco

HFD-530/RPM/Truffa

cc:

IND _____

HFD-530/Division File

HFD-530/Murray

HFD-530/Toerner

HFD-530/RPM/Truffa

Location: V:Drive/DAVDP/CSO/Truffa/IND/IND. — "Salvage.doc

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